EXHIBIT F

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RESEARCH ARTICLES

Pulmonary Function and Pleural Fibrosis: Quantitative Relationships With an Integrative Index of Pleural Abnormalities

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Pleural fibrosis due to asbestos exposure was fully appreciated considerably later than pulmonary interstitial fibrosis due to similar exposure. This is well exemplified by the fact that pleura face on was included in the International Labour Office's International Classification of Radiographs of Pneumoconioses only in the last revision of the Classification. The functional relevance of pleural fibrosis, in particular circumscribed pleural fibrosis, has remained controversial. Since pleural fibrosis can occur at various sites (diaphragmatic plaques, chest wall in profile and face on, mediastinal) and can be of different thickness and extent, a comprehensive integrative assessment of pleural fibrosis was undertaken in order to permit a quantitative study of relationships between pleural fibrosis and pulmonary function. This approach was used for chest X-ray films of 1,584 asbestos insulation workers examined (1981–1983); 1,185 (75%) had pleural fibrosis. The distribution pattern of the integrative pleural index was found to be different in the subgroup with circumscribed (n = 975) from that with diffuse (n = 197) pleural fibrosis, with a higher profusion of high INDEX values in the latter. Stepwise regression analysis indicated that there was a significant inverse relationship between forced vital capacity (FVC) and the integrative index of pleural fibrosis in the subgroup with circumscribed pleural fibrosis. In the subgroup with diffuse pleural fibrosis, the obliteration of costophrenic angle(s), even with pleural fibrosis of limited extent, resulted in marked decrement in FVC % predicted; higher values of INDEX did not result in additional significant reductions of FVC. In those with both parenchymal and pleural abnormalities (n = 862) the pleural index was found to make a significant contribution, independent of that of parenchymal abnormalities, to decrements of FVC. Since pleural fibrosis has gradually become the predominant radiologically detectable abnormality in asbestos exposed workers, establishing its quantifiable functional relevance is useful.

Key words: integrative index of pleural changes, pleural index, asbestos exposure, ILO classification

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INTRODUCTION

The effects of asbestos exposure include interstitial pulmonary fibrosis and pleural fibrosis. Historically, interstitial pulmonary fibrosis has received considerably more attention; over many decades, before the implementation of effective control measures, exposure to high concentrations of asbestos fibers resulted in marked and disabling interstitial pulmonary fibrosis after relatively short periods of time (10 years, and sometimes even less). Although pleural fibrosis was recognized early on as being a potential result of asbestos exposure, it was for many years overshadowed by the severity of the interstitial pulmonary fibrosis with relatively rapid progression and marked functional impairment.

Recognition of the entire spectrum of asbestos-induced adverse effects, including the carcinogenic effects (most importantly the increased incidence of lung cancer and pleural and peritoneal mesothelioma), resulted in a more marked trend towards lowering exposure levels and increased efforts for regulatory action. Recognition of the disease potential of intermittent asbestos exposure (in construction trades, sheetmetal workers, plumbers, etc.,) and of "bystander" exposure due to the mere presence in a work environment where asbestos was used (e.g., all shipyard workers, independent of their trade) increased considerably in the 1970s and 1980s. Thus, the size of industrial populations at risk as a result of such types of exposure expanded considerably, with estimates being of the order of 20 million [Nicholson et al., 1982; Schwartz et al., 1990].

In recent years, an increasing number of investigators have reported higher prevalence rates for pleural abnormalities than for parenchymal pulmonary changes in populations of shipyard workers, maintenance workers in the chemical and oil refinery industries, railroad workers, sheetmetal workers, plumbers, and pipefitters [Felton et al., 1980; Lilis et al., 1980; Baker et al., 1985; Oliver et al., 1985; Sprince et al., 1985; Jarvholm and Sanden, 1986; Lundorf et al., 1987]. The relationship of pleural fibrosis with time from onset of asbestos exposure was recognized; prevalence increased with length of observation.

Multiple recent observations have converged in indicating that pleural fibrosis can be extensive although, in some cases, it can remain quite limited. The recognition of the wide spectrum of possible extent and width of asbestos-induced pleural fibrosis led to the scoring system for pleural changes adopted in the International Classification of Radiographs of Pneumoconioses. It was only in 1980 [ILO, 1980] that pleural fibrosis face on, a quite important component, was included in the Classification.

Although pleural fibrosis has become the abnormality most frequently detected in asbestos exposed persons, for many years there has been an ongoing debate regarding its clinical and functional significance [Baker et al., 1985; Picado et al., 1987]. Some have held the opinion that pleural plaques (or circumscribed pleural fibrosis, according to the International Classification) are merely a marker of asbestos exposure with practically insignificant clinical importance [Hillerdal and Lindgren, 1980; Parkes, 1982; Jones et al., 1988] if not accompanied by interstitial pulmonary fibrosis. Diffuse pleural fibrosis, defined by involvement of the visceral pleura (the parietal pleura can also be thickened), and including blunting of the costophrenic angle, has been generally accepted to result in restrictive pulmonary dysfunction [Miller et al., 1983; McGavin and Sheers, 1984]. Diffuse pleural fibrosis represents only a small proportion of all cases with pleural fibrosis; in most cases (80% or more)

pleural fibrosis is of the circumscribed type. Recent studies have contributed increasing evidence that circumscribed pleural fibrosis may have a negative effect on pulmonary function [Baker et al., 1985; Oliver et al., 1985, 1988; Jarvholm and Sanden, 1986; Hilt et al., 1987; Bourbeau et al., 1988; Schwartz et al., 1990].

Quantification of Asbestos-Induced Pleural Disease

The International Classification of Radiographs of Pneumoconioses [ILO, 1980] categorizes several features of pleural fibrosis to be recorded. These include possible locations of pleural changes (chest wall, diaphragm, other sites, i.e, pericardium and mediastinum), a system for grading the extent and width of the thickened pleura (in profile), as well as a system of grading pleural thickening face on, and a scheme for grading pleural calcifications. Provisions are made for recording the presence of "circumscribed" and "diffuse" pleural fibrosis; there is, nevertheless, no clear definition of diffuse pleural fibrosis in the present International Classification, a fact which has resulted in different groups of investigators using different definitions of diffuse pleural fibrosis.

The fragmented nature of the information on pleural fibrosis presently being collected according to the instructions for the use of the International Classification of Radiographs of Pneumoconioses makes it difficult to study relationships between pleural fibrosis and either symptoms (mainly dyspnea) or pulmonary function. Many investigators have used only the dichotomous information on absence or presence of pleural fibrosis [Baker et al., 1985; Jarvholm and Sanden, 1986]. Others have classified pleural fibrosis as unilateral and bilateral, while also using the categories of circumscribed and diffuse pleural fibrosis [Sprince et al., 1985]. When present, diffuse and circumscribed pleural fibrosis have occasionally been treated separately.

There have been some attempts to integrate different characteristics of pleural fibrosis, in order to improve the assessment of relationships with pulmonary function and dyspnea. Some of these have used only a limited number of components [McGavin and Sheers, 1984]; others required components that were not part of the usual ILO interpretation [Bégin et al., 1984] or used various weighting schemes for the presence of "definite" or "suspected" pleural changes [Oliver et al., 1985] or for pleural calcifications.

The relatively higher prevalence of asbestos-induced pleural abnormalities than that of parenchymal changes in numerous industrial populations studied in recent years and the accumulating evidence that pleural fibrosis can have a detrimental effect on pulmonary function and its clinical correlate, shortness of breath, prompted us to investigate the usefulness of an integrative index of pleural fibrosis (INDEX) in a large population of asbestos exposed insulation workers and to explore its quantitative relationship with pulmonary function. A systematic approach to the construction of such an INDEX, on which agreement could be reached, would allow comparison between results of different epidemiologic studies and contribute a better understanding of the determinants and functional consequences of asbestos-induced pleural fibrosis.

POPULATION AND METHODS

Population

The study population consisted of 1,584 asbestos insulation workers with long-term asbestos exposure (the majority over 30 years). All were members of a large

cohort (17,800 men), of asbestos insulation workers in the United States and Canada established on January 1, 1967 and observed prospectively since. The structure and mortality experience of this cohort 1967–1977 have been reported [Selikoff et al., 1979]. Between July 24, 1981 and November 15, 1983, a comprehensive medical examination was conducted of members of the cohort who had reached 30 years from onset of work and accepted an invitation to participate in a medical survey. Response rate, reasons for non-participation, and other details on the population examined have been recently published [Lilis et al., 1991].

The examinations included lifetime occupational, medical and smoking histories, review of symptoms, respiratory questionnaire [MRC 1960, 1966], physical examination, standard blood and urine laboratory tests, chest X-ray films (postero-anterior and lateral), and spirometric pulmonary function tests adhering to current guidelines [ATS, 1987].

Pleural INDEX

Chest radiographs were interpreted according to the ILO Classification of Radiographs of Pneumoconioses [ILO, 1980]. When the clinical field studies started, in November 1981, the 1980 revision of the International Classification had not yet been made available; since chest X-ray films were interpreted after each field study (in 19 cities in the United States), part of the films were interpreted using the 1970 version of this classification (until the 1980 revision of the International Classification of Radiographs of Pneumoconioses became available). This study is based only on chest X-ray films interpreted following the implementation of the 1980 revision of the ILO Classification of Radiographs of Pneumoconioses (a total of 1,584 films).

The 1980 revision of the International Classification of Radiographs of Pneumoconioses includes several new features, such as the grading of pleural thickening face on, and changes in the grading of extent of pleural fibrosis in profile. It was therefore decided to calculate the pleural INDEX on the 1,584 films read according to the 1980 revision of the classification.

The following approach was used to obtain pleural INDEX:

1. for each hemithorax, for pleural thickening in profile, the width A, B, or C was coded 1, 2, or 3, respectively.
2. the extent score (1, 2, or 3) was multiplied by the figure for width.
3. for pleura face on, the extent (1, 2, or 3) was multiplied by a factor of 2 (since width of pleura face on cannot be measured, the median possible width was assumed); the product was added to that obtained for pleural thickening in profile.
4. diaphragmatic plaques were given a score of 1 (if measuring less than 2 cm) or 2 (more than 2 cm); this figure, as well as the grading for pleural calcifications (1, 2, or 3), were added to the score obtained for chest wall pleural thickening.

The approach used can be summarized as follows:

$$\text{Integrative pleural index (one hemithorax)} = W(1, 2, \text{or } 3) \times E(1, 2, \text{or } 3) + 2F(1, 2, \text{or } 3) + P(1 \text{ or } 2) + C(1, 2, \text{or } 3)$$

where W is the width of pleural thickening in profile; E is the extent of pleural thickening in profile; F is pleural thickening face on; P is diaphragmatic plaque; and C is pleural calcification.

The totals obtained for the right and left hemithorax were added to give the pleural INDEX (possible maximum value of 40).

Diffuse pleural fibrosis, defined as that which includes blunting of the ipsilateral costophrenic angle, was indicated with the symbol D. For certain analyses, circumscribed pleural fibrosis was treated separately from diffuse pleural fibrosis.

This pleural INDEX is based only on items recorded within the framework of the current International Classification of Radiographs of Pneumoconioses; it is comprehensive, including all components that might be important, such as pleural thickening face on, diaphragmatic pleural plaques, and pleural calcifications with all possible locations (weighting of components was, by necessity, arbitrary, although guided by plausibility).

Statistical Methods

Pearson correlation coefficients were used to measure the correlation between continuous variables, such as duration from onset of exposure, smoking pack years, age, and profusion score of small opacities. Since the distribution of values for the pleural INDEX was positively skewed, a logarithmic transformation was applied to these data to provide a more symmetric distribution. Multiple regression methods were employed to examine the relationships between forced vital capacity (FVC) and explanatory variables such as the logarithm of the pleural index, as well as to examine the relationship between the pleural index and variables such as years from first exposure to asbestos. In performing these analyses, model selection was done by comparing results of backwards stepwise methods and results of all-possible-subsets methods [Wetherill, 1986]. These techniques were implemented with procedures STEPWISE, RSQUARE, and REG in SAS [SAS, 1985]. In the all-possible-subsets analyses, the adjusted R-square was used as a criterion for model selection. In practically all instances, the different approaches gave identical models. Where there were differences, simplicity of the form of the model without loss of value in the adjusted R-square was the principle used for choosing a model.

RESULTS

Of the total of 1,584 chest X-ray films of insulation workers with long-term exposure included in this study, 1,185 (75%) showed evidence of pleural fibrosis. The pleural INDEX was calculated as indicated in Population and Methods. The logarithm of the INDEX was used in all statistical analyses since the distribution of the values was skewed to the right (Fig. 1). Stepwise multiple regression analysis showed that years since first asbestos exposure was the only variable that significantly correlated with the pleural INDEX (Table I); age, years exposed, and smoking were the other variables tested. The geometric mean of INDEX for all 1,185 cases with pleural fibrosis was 5.81, with 80% of values ≤ 12.

There were differences between the distribution pattern of the pleural index in the subgroup with parenchymal abnormalities (small irregular opacities) and the subgroup without radiologically detectable parenchymal ($\geq$ 1/0) changes (Fig. 2). The proportion of those without pleural changes (INDEX = 0) was higher in the subgroup without than in that with parenchymal abnormalities (35% vs. 16%). The proportion of cases with an INDEX ≥ 12 was more than double in those with parenchymal abnormalities than in the subgroup without such changes (8% vs. 1.5%).

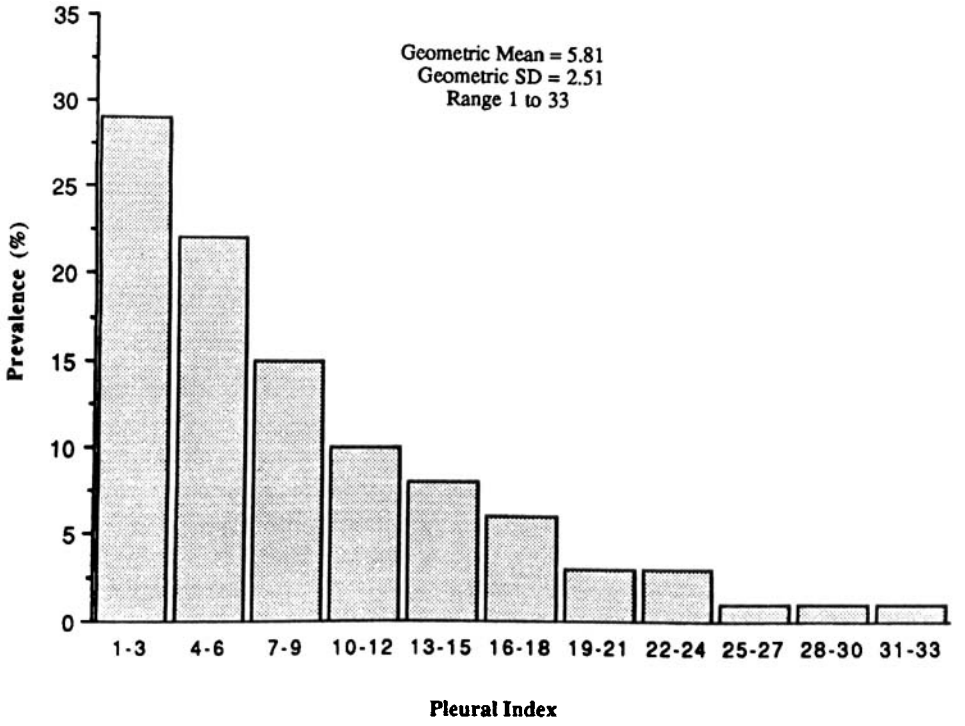

Fig. 1. Distribution pattern of integrative index of pleural fibrosis, N = 1,185.

TABLE I. Stepwise Multiple Regression of Integrative Index of Pleural Fibrosis*

Explanatory variable	Regression coefficient ±SE	t-Statistic	p-Value
Intercept	1.19	—	
Years since first exposure	.026 (.004)	7.038	.0001

*Age, years exposed, years from onset of exposure, and smoking (pack year) were the variables tested. Log index (calculated on non-zero index values) was used in the analysis.

The distribution of the INDEX was found to differ considerably between the smaller subgroup of 210 persons with diffuse pleural fibrosis and the much larger subgroup with circumscribed pleural fibrosis (Fig. 3). In those with circumscribed pleural fibrosis, the distribution of INDEX was very similar to that for all pleural fibrosis (Fig. 1), markedly skewed, with lower values ($\leq$12) in more than three-fourths of the total subgroup; the geometric mean was 5.06. In the subgroup with diffuse pleural fibrosis, the distribution of INDEX had a completely different pattern, with a much higher proportion of cases (over 50%) having an elevated INDEX (>12); the geometric mean was 10.97.

Mean values (±SD) for FVC % predicted were calculated for subgroups of

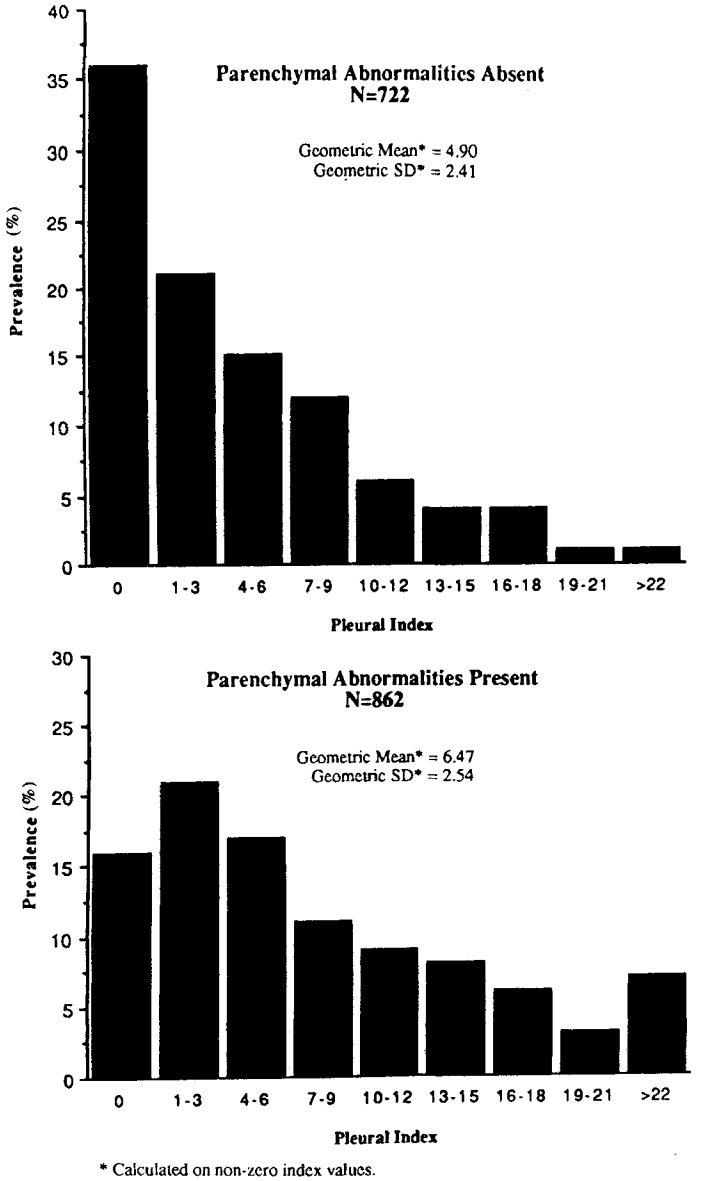

Fig. 2. Distribution of integrative index of pleural fibrosis.

ascending pleural INDEX values. A gradual decrease of FVC % predicted with increasing index was observed, from FVC 89% predicted in those without pleural fibrosis (INDEX = 0), to 83% for INDEX 1–3 and 4–6, and 71% for those with INDEX ≥22 (Fig. 4).

Gradual decrements of mean FVC % predicted with increasing pleural INDEX were found in both subgroups, with and without radiologically detectable parenchymal abnormalities; as expected, the decrements were more marked in the subgroup

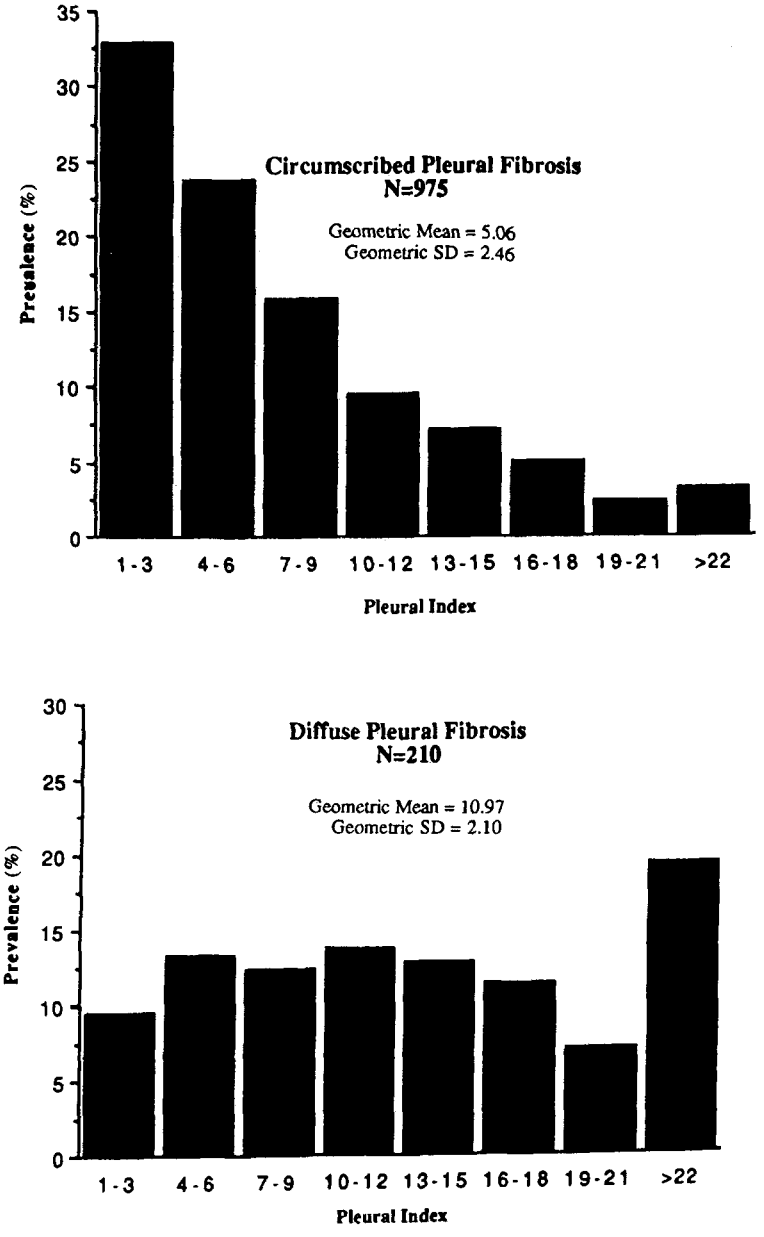

Fig. 3. Distribution pattern of integrative index of pleural fibrosis.

with both parenchymal and pleural fibrosis (Fig. 5) for all subgroups of INDEX values.

Multiple regression analysis of FVC % predicted showed that the pleural INDEX was a significant variable contributing to decrement in FVC % predicted in the subgroup without radiologically detectable parenchymal opacities; other variables

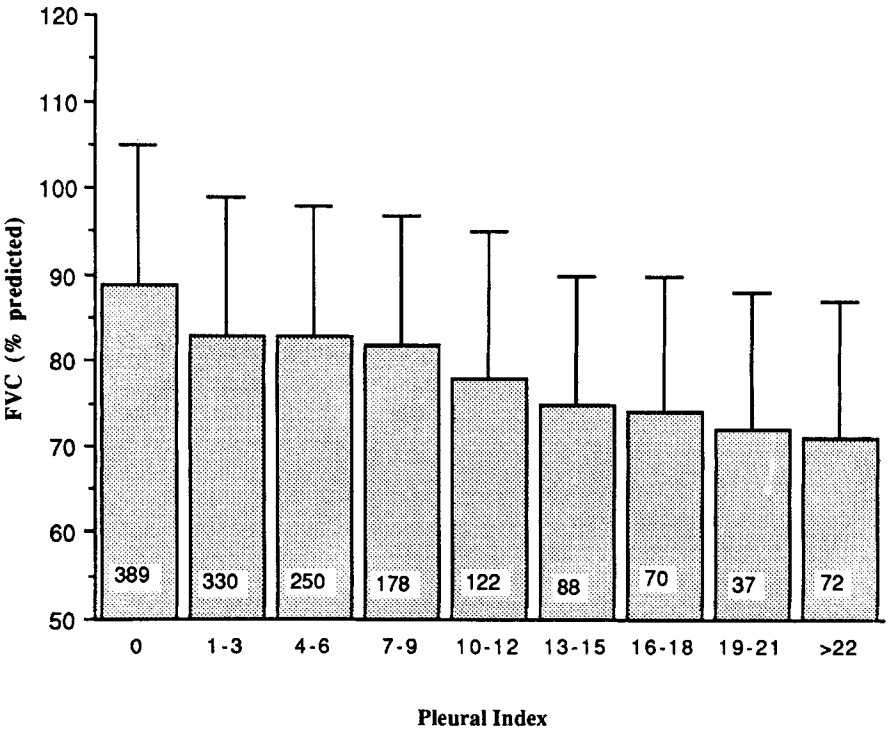

Fig. 4. Relationship between FVC and integrative index of pleural fibrosis, N = 1,536.

with a significant negative effect on FVC were years since first exposure and cigarette smoking (pack year). In the subgroup with both parenchymal and pleural abnormalities, the pleural index was found to be a significant variable, independent of parenchymal abnormalities, contributing to decrement in FVC; years since first exposure and cigarette smoking were again found to be significant variables (Table II).

Mean values of FVC % predicted were calculated for ascending pleural index values in the subgroups with circumscribed pleural fibrosis and diffuse pleural changes. In those with circumscribed pleural fibrosis, gradual decrements in mean FVC were seen with increasing INDEX values. In the subgroup with diffuse pleural fibrosis, gradual decrements in mean FVC % predicted were not noted. Even the lowest pleural index was associated with a considerably reduced mean FVC (69% predicted); increasing values of the INDEX did not seem to have a considerable negative affect on FVC % predicted (Fig. 6).

Stepwise regression analysis on the subgroup with circumscribed pleural fibrosis showed a significant ($p < .0001$) inverse relationship between FVC and INDEX, after adjustment for the independent effects of duration from onset of exposure, parenchymal abnormalities (profusion of small opacities), and cigarette smoking (Table III). Regression analysis was also performed on the subgroup with diffuse pleural fibrosis (N = 197). Pleural index did not reach the level of statistical significance; years since first exposure and profusion of small opacities were significant variables associated with FVC in an inverse manner. These results are consistent with the well known and generally accepted fact that diffuse pleural fibrosis has a more

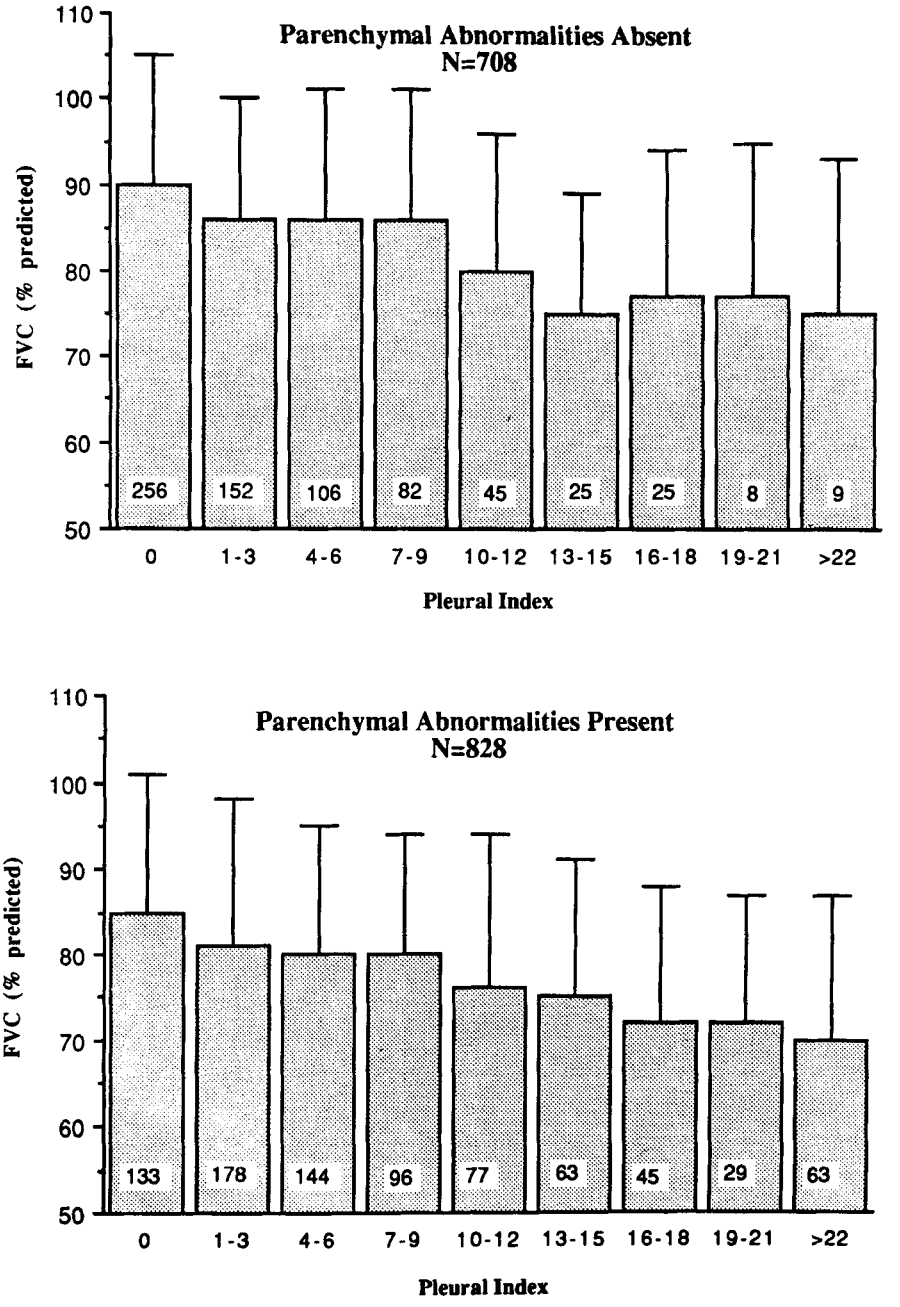

Fig. 5. Relationship between FVC and integrative index of pleural fibrosis.

marked effect on pulmonary function, i.e., FVC % predicted. The data seem to indicate that blunting of the costophrenic angles, even with little additional diffuse pleural fibrosis, has the effect of considerably reducing FVC.

TABLE II. Multiple Regression of FVC % Predicted Subgroup With Pleural and Parenchymal Abnormalities (n = 695)

Variable	Coefficient (±SE)	t-Statistic	p-Value
Intercept	105.39 (3.48)		
Years since first exposure (DURONSET)	.34 (.09)	−3.93	.0001
Pack year	−.06 (.02)	−3.05	.0024
Profusion of small opacities (PROFUSION)	−6.75 (1.24)	−5.44	.0001
Pleural index (log index)2	−1.02 (.18)	−5.59	.0001

R^2 = .137

		Correlations	
		DURONSET	Pack year
Age (years) (mean ± SD)	60.4 ±7.9	Pleural index .22	−.10
DURONSET (years) (mean ± SD)	37.2 ±6.9	PROFUSION .11	.13
		DURONSET	−.07
		Age .73	.07

Multiple Regression of FVC % Predicted Subgroup With Pleural Abnormalities Only (n = 452)

Variable	Coefficient (±SE)	t-Statistic	p-Value
Intercept	102.16 (3.61)		
Years since first exposure (DURONSET)	−.36 (.10)	−3.57	.0004
Pack year	−.08 (.03)	−3.22	.0014
Pleural index (log index)2	−1.18 (.26)	−4.52	.0001

R^2 = .093

		Correlations	
		DURONSET	Pack year
Age (years) (mean ± SD)	56.7 ± 7.6	Pleural index .10	−.08
DURONSET (years) (mean ± SD)	34.5 ± 7.0	DURONSET	−.02
		Age .77	.04

The relationship between profusion of small opacities and FVC % predicted is well recognized and generally accepted. To provide a side by side comparison of: 1) how the INDEX relates to FVC % predicted; and 2) how profusion of small opacities relates to FVC % predicted, the equations in Table IV were generated. These simple models relate INDEX and profusion score separately to FVC % predicted. Then the following questions were asked: 1) What values of the INDEX predict FVC %s of 90%, 85%, 80%, and 75%? 2) What values of the profusion score

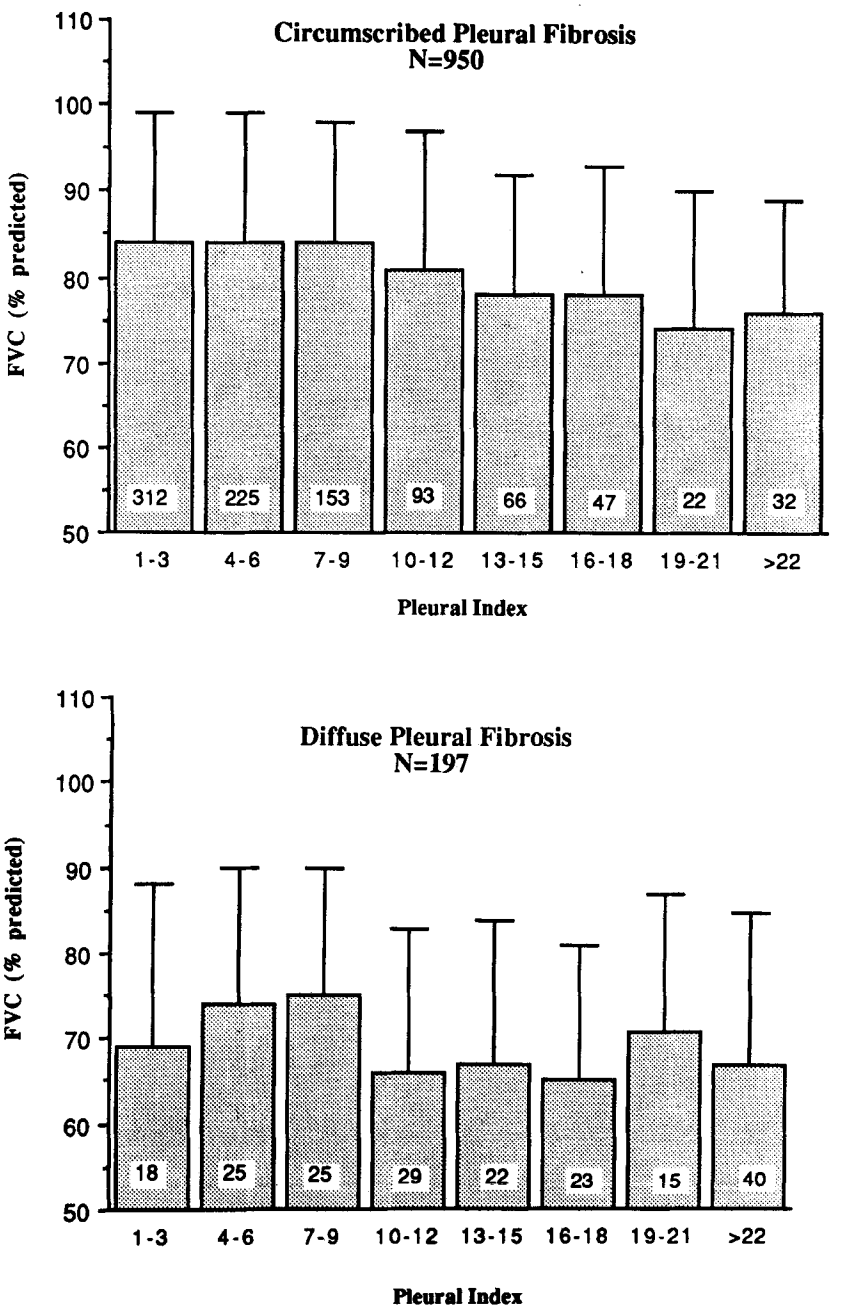

Fig. 6. Relationship between FVC and integrative index of pleural fibrosis.

predict FVC %s of 90%, 85%, 80%, and 75%? From Table IV, we see, for example, that an INDEX value of 5 corresponds to an FVC % predicted of 85%, in the absence of parenchymal abnormalities; and conversely, a profusion score of 1/1 also predicts an FVC % of 85%, in the absence of pleural abnormalities.

TABLE III. Multiple Regression of FVC % Predicted Subgroup With Circumscribed Pleural Fibrosis (n = 950)

Variable	Coefficient (±SE)	t-Statistic	p-Value
Intercept	98.84 (2.54)		
Years since first exposure (DURONSET)	−.27 (.07)	−3.81	.0001
Pack year	−.08 (.02)	−4.71	.0001
Profusion of small opacities (PROFUSION)	−2.84 (.74)	−3.84	.0001
Pleural index (log index)2	−.72 (.17)	−4.27	−.0001
	R^2 = .0932		

Multiple Regression of FVC % Predicted Subgroup With Diffuse Pleural Fibrosis (n = 197)

Variable	Coefficient (±SE)	t-Statistic	p-Value
Intercept	96.75 (7.12)		
Years since first exposure (DURONSET)	−.48 (.17)	−2.90	.0042
Pack year	.0014 (.04)	.035	.9723
Profusion of small opacities (PROFUSION)	−4.19 (1.64)	−2.55	.0114
Pleural index (log index)2	−.69 (.39)	−1.79	.0750
	R^2 = .1051		

DISCUSSION

The relatively higher prevalence, in recent large studies of asbestos exposed workers, of radiologically detectable pleural fibrosis than that of parenchymal interstitial pulmonary fibrosis, has made it necessary and important to objectively assess the possibility of an independent effect of pleural fibrosis on pulmonary function.

It is well known from comparisons of radiographic findings with those obtained at post mortem examinations, that pleural fibrosis is in many cases more extensive than recognized on the standard chest X-ray. The use of computerized tomography (CT) of the chest in recent years has also shown that pleural fibrosis, as revealed on the CT scan, is often more extensive than that seen on the standard chest X-ray film. It thus is generally accepted that detection of pleural fibrosis on the standard PA chest X-ray is incomplete. Nevertheless, for practical purposes, detection of adverse effects of past asbestos exposure in populations (often of considerable size) still relies to a

TABLE IV. Decrements in FVC % Predicted and the Corresponding Increments of Pleural INDEX or Profusion of Small Opacities

A: Effect of Pleural Index*

Parenchymal abnormalities absent		Parenchymal abnormalities present	
FVC % predicted = $89.62 - 1.44 \times [\text{Log (INDEX} + 1)]^2$		FVC % predicted = $84.53 - 1.37 \times [\text{Log (INDEX} + 1)]^2$	
FVC % predicted	INDEX	FVC % predicted	INDEX
89.62	0		
85	5.0	84.53	0
80	12.3	80	5.2
75	23.2	75	13.0
70	> 33.0	70	25.0
		65	> 33.0

B: Effect of Profusion of Small Opacities

Pleural abnormalities absent		Pleural abnormalities present	
FVC % predicted = $90.63 - 5.13 \times$ CPAR[a]		FVC % predicted = $84.46 - 5.98 \times$ CPAR[a]	
FVC % predicted	CPAR[a]	FVC % predicted	CPAR[a]
90.63	0		
85	1.1	84.46	0
80	2.1	80	.8
75	3.1	75	1.6
		70	2.4
		65	3.3

*Log (INDEX + 1) has been used because individuals with INDEX = 0 were included in deriving these equations.
[a]Profusion score of small opacities.

large extent on the correct interpretation of the standard chest X-ray film, according to the International Classification of Radiographs of Pneumoconioses.

The present study originated in the perceived need for a comprehensive quantitative assessment of pleural fibrosis on the standard chest X-ray film in order to better characterize and quantitatively evaluate its effect on pulmonary function.

Several studies have addressed the need to integrate the different characteristics of pleural fibrosis, as coded by the ILO Classification; different approaches have been used in order to better explore relationships with outcomes such as dyspnea and/or pulmonary function decrements. An early proposed radiographic score for pleural fibrosis recommended using 1 or 0 for presence or absence of costophrenic angle obliteration, to which the extent of pleural thickening (1, 2, or 3) for each side of the chest was to be added; a maximum score of 4 for each hemithorax and of 8 for an entire film was thus possible [McGavin and Sheers, 1984]. While such an attempt at integrating information on pleural fibrosis has the advantage of being simple, it omits many important components such as pleural fibrosis face on, diaphragmatic plaques (often extensive), and pleural calcifications.

Some other approaches to construct a score for total pleural fibrosis have included elements not recorded in the International Classification of Radiographs of Pneumoconioses, such as the thickness of diaphragmatic plaques and that of costophrenic angles, as well as their respective extents [Bégin et al., 1984]; application to large studies in which chest X-ray films have been interpreted according to the ILO Classification would require re-reading the films, and would therefore be impractical.

Others have calculated pleural scores by giving increasing weight to increasing thickness or extent of pleural fibrosis; the presence of pleural calcifications was at times considered as a factor doubling the score [Green et al., 1984]. Another approach added the scores for extent to those for width of pleural thickening and to diaphragmatic plaques; the sum was multiplied by 2 when the pleural changes were definite [Oliver et al., 1985, 1988].

In this study, we have used a comprehensive approach to the construction of a pleural INDEX, in which all pertinent components of the ILO classification are included. The large size of the population studied has allowed the characterization of the pleural fibrosis INDEX distribution pattern in those with and without coexistent radiologically detectable interstitial pulmonary fibrosis. The larger proportion of high values for the pleural INDEX in those with coexistent parenchymal interstitial fibrosis is in agreement with previous findings.

A differential distribution pattern of the pleural INDEX in those with circumscribed pleural fibrosis as compared with the diffuse pleural fibrosis subgroup was detected: in the subgroup with circumscribed fibrosis, the INDEX had a skewed distribution, with a higher proportion of relatively low values. In the smaller subgroup of diffuse pleural fibrosis, there was a rather even distribution pattern, with proportionally more cases with high values of the INDEX (extensive pleural fibrosis).

Both types of pleural fibrosis, diffuse (with obliteration of the costophrenic angle) and circumscribed, were found to have a negative effect on FVC % predicted. Decrements in FVC were more marked in those with diffuse pleural fibrosis, at every level of magnitude of the pleural INDEX. These findings confirm previous observations regarding the more marked functional impact of diffuse pleural fibrosis.

In the subgroup with circumscribed pleural fibrosis, multiple regression analysis showed that the pleural INDEX had a statistically significant and independent (of profusion of small opacities) effect on FVC % predicted. Thus, the overall extent of pleural fibrosis, expressed in the integrative INDEX, was shown to have a quantifiable decremental effect on FVC: the higher the INDEX and the more extensive the circumscribed pleural fibrosis, the lower the FVC.

In the subgroup with diffuse pleural fibrosis, the magnitude of the pleural INDEX did not significantly affect FVC; it was the presence of the blunted costophrenic angle, even when accompanied by only very limited pleural fibrosis, that had the most decisive effect in reducing FVC % predicted.

Although the possibility of parenchymal interstitial fibrosis not yet radiologically detectable in some cases cannot be completely excluded with the methodology used in our study, the quantitative relationships presented would have been highly improbable in the absence of an independent effect of pleural fibrosis.

An increasing number of studies have, in recent years, explored the effects of asbestos-induced pleural fibrosis on spiromteric measurements of lung function, more specifically on FVC. Most of these studies have reported findings concordant with ours, indicating a restrictive effect of pleural fibrosis. In many instances, the distinc-

tion between circumscribed and diffuse pleural fibrosis was not made; in other studies, only circumscribed pleural fibrosis was reported [Jarvholm and Sanden, 1986; Oliver et al., 1985]. The fact that a majority of cases with pleural changes, about 80% in most populations studied [Schwartz et al., 1990], was represented by circumscribed pleural fibrosis explained the similarity of findings in studies in which the distinction between circumscribed and diffuse pleural fibrosis was not made [Baker et al., 1985; Bourbeau et al., 1988]. Only in very few large recent studies have there been attempts to quantify the restrictive effect of circumscribed pleural fibrosis [Schwartz et al., 1990]; it was shown to have a significant effect, although diffuse pleural fibrosis had a more marked restrictive effect.

Our study documents the quantitative relationship between the extent of circumscribed pleural fibrosis and the restrictive effect on pulmonary function, and thus contributes to a more complete understanding of the biologic and functional significance of asbestos-induced pleural fibrosis. Since circumscribed pleural fibrosis represents about 80% of all pleural fibrosis due to asbestos, firmly establishing its functional relevance is of considerable importance.

REFERENCES

American Thoracic Society (1987): Standardization of spirometry—1987 update. Am Rev Respir Dis 136:1285–1298.

Baker EL, Dagg T, Greene RE (1985): Respiratory illness in the construction trades. The significance of asbestos-associated pleural disease among sheet metal workers. J Occup Med 27:483–489.

Bégin R, Boctor M, Bergeron D, Cantin A, Berthiaume Y, Péloquin S, Bisson G, Lamoureux G (1984): Radiographic assessment of pleuropulmonary disease in asbestos workers: posteroanterior, four view films, and computed tomographs of the thorax. Br J Ind Med 41:373–383.

Bourbeau J, Ernst P, Chrome J, Nunes F, Armstrong B, Blanchet Y, Becklake MR (1988): Relationship between respiratory impairment and asbestos related pleural disease in an active workforce. Am Rev Respir Dis 137:92 (suppl).

Felton JS, Sargent EN, Gordonson JS (1980): Radiographic changes following asbestos exposure: experience with 7,500 workers. J Occup Med 22:15–20.

Greene R, Boggis C, Jantsch H (1984): Asbestos-related pleural thickening: effect of threshold criteria on interpretation. Radiology 152:569–573.

Hillerdal G, Lindgren A (1980): Pleural plaques: correlation of occurrence at autopsy to radiographic findings and occupational history. Eur J Respir Dis 61:315–318.

Hilt B, Lien JT, Lund-Larsen PG (1987): Lung function and respiratory symptoms in subjects with asbestos-related disorders: a cross-sectional study. Am J Ind Med 11:517–528.

The ILO International Classification of Radiographs of Pneumoconioses. Geneva: International Labour Office (1980): Occupational Safety and Health Series No. 22 (revised).

Jarvholm B, Sanden A (1986): Pleural plaques and respiratory function. Am J Ind Med 10:419–426.

Jones RN, McLoud T, Rockoff D (1988): The radiographic pleural abnormalities in asbestos exposure: relationship to physiological abnormalities. J Thorac Imaging 3(4):57–66.

Lilis R, Daum S, Anderson H, Andrews G, Selikoff IJ (1980): Asbestosis among maintenance workers in the chemical industry and in oil refinery workers. In Wagner JC (ed): "Biological Effects of Mineral Fibres," Vol 2. Lyon: IARC Sci Publ No 30; pp 795–810.

Lilis R, Miller A, Godbold J, Chan E, Selikoff IJ (1991): Radiographic abnormalities in asbestos insulators: effects of duration from onset of exposure and smoking. Relationships of dyspnea with parenchymal and pleural fibrosis. Am J Ind Med 20:1–17.

Lundorf E, Aagaard MT, Andresen J, Silberschmid M, Sabro S, Coutte A, Bolvig L (1987): Radiological evaluation of early pleural and pulmonary changes in light asbestos exposure. Am J Respir Dis 70:145–149.

McGavin CR, Sheers G (1984): Diffuse pleural thickening in asbestos workers: disability and lung function abnormalities. Thorax 39:604–607.

Medical Research Council (1960): Standardized questionnaire on respiratory symptoms. Br Med J 2: 1665.

Medical Research Council's Committee on Research into Chronic Bronchitis (1966): "Instructions for the Use of the Questionnaire on Respiratory Symptoms." London: MRC.

Miller A, Teirstein AS, Selikoff IJ (1983): Ventilatory failure due to asbestos pleurisy. Am J Med 75:911–919.

Nicholson WJ, Perkel G, Selikoff IJ (1982): Occupational exposure to asbestos: population at risk and projected mortality—1980–2030. Am J Ind Med 3:259–311.

Oliver LC, Eisen EA, Greene RE, Sprince L (1985): Asbestos-related disease in railroad workers. Am Rev Respir Dis 131:499–504.

Oliver LC, Eisen EA, Greene R, Sprince NL (1988): Asbestos-related pleural plaques and lung function. Am J Ind Med 14:649–656.

Parkes RW (1982): Silicates and lung disease. In Parkes RW (ed): "Occupational Lung Disorders." Boston: Butterworth & Co, pp 233–332.

Picado C, Laporta D, Grassino A, Cosio M, Thibodeau M, Becklake M (1987): Mechanisms affecting exercise performance in subjects with asbestos-related pleural fibrosis. Lung 165:45–57.

SAS User's Guide (1985): Statistics. In Stanish WM, Sall JP: "PROC, CATMOD" in 5th Ed. Cary, NC: SAS Institute Inc., pp 171–254.

Schwartz DA, Fuortes LJ, Galvin JR, Burmeister LF, Schmidt LE, Lestikow BN, Lamarte FP, Merchant JA (1990): Asbestos-induced pleural fibrosis and impaired lung function. Am Rev Respir Dis 141:321–326.

Selikoff IJ, Hammond EC, Seidman H (1979): Mortality experience of insulation workers in the United States and Canada. Ann NY Acad Sci 330:91–116.

Sprince NL, Oliver LC, McLoud TC (1985): Asbestos-related disease in plumbers and pipefitters employed in building construction. J Occup Med 27:771–775.

Wetherill GB (1986): "Regression Analysis with Applications." New York: Chapman and Hall, p 237.